PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15660PCT00	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/DK2005/000218	International filing date *(day/month/year)* 30.03.2005	Priority date *(day/month/year)* 30.03.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K38/00 A61K39/00 G01N33/53 A61P35/00		
Applicant DEN KGL.VETERINAER-OG LANDBOHOJSKOLE et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 12 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand 27.01.2006	Date of completion of this report 22.06.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Schönwasser, D Telephone No. +49 30 25901-318

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2005/000218

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-43 as originally filed

Sequence listings part of the description, Pages

1 as originally filed

Claims, Numbers

1-47 as originally filed

Drawings, Sheets

1/6-6/6 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-23,27-29,38,39 (partially)

because:

☒ the said international application, or the said claims Nos. 1-23,27-29,38,39 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 1,5 (partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☐ neither restricted the claims nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-47
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-47
Industrial applicability (IA)	Yes:	Claims	24-26,30-37,40-47
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

   see separate sheet

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

It is noted that the applicant's comments filed with the letter dated 27.01.2006 have been taken into account for establishing the present report.

Re Item III.

1. Present claim 1 relates to a method defined by reference to a desirable characteristic or property, namely the desirable characteristic of said method to be able to increase susceptibility of malignant cells to an anti-cancer therapy. The claim covers all methods having this characteristic or property, whereas the application provides support within the meaning of Article 6, PCT and disclosure within the meaning of Article 5, PCT for only a very limited number of such methods. In the present case, the claim so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6, PCT). An attempt is made to define the method **by reference to a result to be achieved, instead of mentioning the technical features, which are necessary to obtain the desired effect.** Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, namely those parts relating to the methods as mentioned in claims 2-8.

2. Present claim 5 relates to a method claim involving an extremely large number of possible compounds. In fact, the claims contain so many options (e.g. "low molecular weight molecule", "natural products"...) that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely the methods involving blockers as disclosed in the examples 1-8.

3. Claims 1-23,27-29,38 and 39 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV.

The application lacks unity of inventions as required by Article 3(4)(iii) and 17(3)(a) PCT for the following reason:

The inventions as defined in the International Search Report relate to methods of treatment of cancer by use of any molecule having a blocking effect on protease inhibitors, to methods of diagnosis and to methods of screening for blockers of protease inhibitors or for anti-cancer treatments.

The common concept underlying the present application is the recognition that high protease inhibitor levels correlate with cancer and reduction of said high levels of protease inhibitors constitutes an anti-cancer treatment.

Contrary to the applicant's suggestion on p. 2, paragraph 4 of the letter dated 27.01.2006, "the finding that there exists an interplay between tumour tissue expression of metalloproteases and susceptibility of tumour cells to apoptosis" cannot be accepted as novel, inventive, common concept, because e.g. none of the independent claims mentions tumour tissue expression of **metalloproteases**.

Hence, the recognition that high protease inhibitor levels correlate with cancer and reduction of said high levels of protease inhibitors constitutes an anti-cancer treatment is already known in the art (please see e.g. US2002012950, examples 6 and 7 or WO02086085, passages [90-104]).

In light of this prior art the above mentioned common concept is not novel and the problem underlying the present application can be redefined as:

The provision of
(a) methods of anti-cancer treatment by blocking of high protease inhibitor levels
(b) methods of diagnosis by detecting high protease inhibitor levels
(c) methods of screening anti-cancer agents or treatments for blockage of high protease inhibitor levels.

Due to the fact that it is recognized in the prior art that high protease inhibitor levels correlate with cancer and reduction of said high levels of protease inhibitors constitutes an anti-cancer treatment and due to the fact that no other technical feature can be distinguished which, in the light of the prior art, could be regarded as a special technical feature in the sense of Rule 13.2 PCT, there is no single general inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT.

Consequently, the application lacks unity of invention and the different inventions are as formulated as the different subjects in the International Search Report.

Re Item V.

Reference is made to the following documents:

D1: US 2002/012950 A1 (NIELSEN LARS S ET AL) 31 January 2002 (2002-01-31)

D2: WO 02/086085 A (BAYER CORPORATION; MORPHOSYS AG) 31 October 2002 (2002-10-31)

D3: WO 03/000671 A (WYETH) 3 January 2003 (2003-01-03)

D4: SCHROHL ANNE-SOFIE ET AL.: "Tumor tissue concentrations of the proteinase inhibitors Tissue Inhibitor of Metalloproteinases-1 (TIMP-1) and Plasminogen Activator Inhibitor type 1 (PAI-1) are complementary in determining prognosis in primary breast cancer" MOLECULAR AND CELLULAR PROTEOMICS, vol. 2, no. 3, March 2003 (2003-03), pages 164-172, XP002319535

D5: WO 00/62070 A (HOLTEN-ANDERSEN, MADS; STEPHENS, ROSS, W; NIELSEN, HANS, JOERGEN; CHRI) 19 October 2000 (2000-10-19)

D6: WO 02/34776 A (K.U.LEUVEN RESEARCH AND DEVELOPMENT) 2 May 2002 (2002-05-02)

D7: US-A-5 643 752 (HAWKINS ET AL) 1 July 1997 (1997-07-01)
D8: US 2004/014190 A1 (LAWRENCE DANIEL A ET AL) 22 January 2004 (2004-01-22)

1. Novelty and inventive step (Art. 33(2)(3), PCT)

1.1.1 D1 discloses anti-PAI-1 antibodies, which block PAI-1 function, for measuring PAI-1 expression levels and for predicting tumor fate as well as the use of said antibodies for combinatorial cancer treatment ([77-87][108-116], examples 6 and 7).

1.1.2 D2 claims TIMP-1 antibodies in combinatorial therapy against cancer and for use in diagnosis of cancer ([03-08],[85-86],[90-104]).

1.1.3 D3 describes the utility of substituted naphthyl benzofuran derivatives as inhibitors of plasminogen activator inhibitor-1 (PAI-1) and as therapeutic compositions for treating, e.g. cancer. Further, methods of screening for PAI-1 inhibitors are also mentioned (page 1, lines 4-8, page 10, line 13-page 12, line 7; page 19, line 21-page 21, line 38).

1.1.4 D4 reports that expression levels of TIMP-1 and PAI-1 can be used as diagnostic means for breast cancer (page 165, column 1, line 44-column 2, line 23; page 169, column 2, lines 1-19).

1.1.5 D5 claims methods of diagnosis of colorectal cancer by determining expression levels of TIMP-1 (example 6, claims 1-9) .

1.1.6 D6 discloses methods of screening for PAI-1 blocking agents (here PAI-1 antibodies) and their use for treatment of cancer (page 2, lines 19-27; page 7, line 22-page 8, line 5; page 9, line 31-page 10, line 16).

1.1.7 D7 discloses TIMP-4 blockers for use against cancer and methods of screening for TIMP-4 inhibitors (e.g. antibodies). Further, methods of diagnosis of cancer by

determining expression levels of TIMP-4 are mentioned (column 17, line 50-page 19, line 10; column 21, line 62-column 22, line 57; column 25, lines 7-20).

1.1.8 D8 describes methods of screening for i.a. PAI-1 inhibitors. The monoclonal PAI-1 antibody MA-33B8, which is also mentioned in the present description, was identified as a PAI-1 blocker. The use of PAI-1 blockers for treating cancer is also disclosed (passages [32-35],[64],[104-108]).

1.2 Invention 1

Invention 1 relates to methods for improving the effect of an anti-cancer therapy in a patient by blocking a protease inhibitor, preferably the protease inhibitors PAI-1 or TIMP-1, to methods for an anti-cancer treatment of a cancer patient involving the measurement of expression levels of protease inhibitors and to the use of a blocker of a protease inhibitor for the preparation of a pharmaceutical preparation for enhancing the effect of anti-cancer therapy.

In view of information discloses in documents D1-D3 and D6-D8, subject-matter of present claims 1-18, 27-29 and 40-47 is not novel and cannot be regarded as involving an inventive step (Art. 33(2)(3), PCT).

With respect to the applicant's comment on p. 3, paragraph 4 (letter of 27.01.2006), it is pointed out, that even if the combinatorial treatment as disclosed in D1 and D2 is disregarded, the above mentioned claims would lack inventive step, as long as no special effect (e.g. a synergistic effect) has been shown by the claimed combination of two known cancer treatments (here: any cancer treatment plus PAI-1/TIMP-1 antibody treatment).

1.3 Invention 2

Invention 2 refers to methods for predicting whether a cancer patient will benefit from an anti-cancer therapy and to methods for an anti-cancer treatment of a cancer

patient, wherein all said diagnostic methods involve the determination of protease inhibitor expression levels.

With regard to documents D1 (especially example 7, paragraph [0194]), subject-matter of claims 19-29 is not novel and also lacks an inventive step (Art. 33(2)(3), PCT).

1.4 Invention 3

Invention 3 refers to methods for identifying an agent that blocks the anti-apoptotic effect of a protease inhibitor and to methods for identifying an anti-cancer treatment involving the use of a blocker of a protease inhibitor.

Contrary to the applicant's comment on p. 5, paragraph 42 (letter dated 27.01.2006), the claims of invention 3 (claims 30-39) do not relate to the correlation between apoptosis induction and tissue expression levels of inhibitors of metalloproteases. None of the claims mentions tumour tissue expression of **metalloproteases**.

In view of documents D1, D3 and D5-D7, subject-matter of present claims 30-39 is not novel and does not involve an inventive step (Art. 33(2)(3), PCT).

1.5 For the assessment of the present claims 1-23,27-29,38 and 39 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII.

2. Clarity and disclosure (Art, 5,6, PCT)

2.1 The relative terms "such as" used e.g. in claim 5 leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.
Preferred embodiments have to be formulates as dependent claims (see also claim 4; Rule 6.4, PCT)

2.2 Claim 43 is unclear since it refers to "agents defined in claim 1". Claim 1, however, does not define any agents (Art. 6, PCT).